IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE HONORABLE BOARD OF
PATENT APPEALS AND INTERFERENCES

In re Application of Joseph ROBERTS *et al.*
Application No.: 09/972,245
Filing Date: October 9, 2001
Docket No.: 078728-0104

For: **PROTECTING THERAPEUTIC COMPOSITIONS FROM HOST-MEDIATED INACTIVATION**

BRIEF ON APPEAL

Appeal from Group 1635

FOLEY & LARDNER LLP
3000 K Street, N.W.
Washington, DC 20007-5109

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I. REAL PARTY IN INTEREST

The named inventors of the above-captioned application have assigned all rights, title, and interest in the invention to the University of South Carolina.

II. RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences.

III. STATUS OF CLAIMS

Pending claims: 1-6, 11-13, 17-22, 41-42 and 44.

Withdrawn claims: 47-64.

Cancelled claims: 7-10, 14-16, 23-40, 43, 45-46.

Rejected claims: 1-6, 11-13, 17-22, 41-42 and 44.

Appealed claims: 1-6, 11-13, 17-22, 41-42 and 44.

IV. STATUS OF AMENDMENTS

In the Office Action dated June 23, 2009, the PTO entered and considered all of the amendments set forth in the Amendment and Reply Under 37 C.F.R. §1.116 that was filed on May 20, 2009. No amendments were submitted after the Office Action of June 23, 2009.

V. SUMMARY OF CLAIMED SUBJECT MATTER

Independent claim 1 is directed to a method for determining the type of biocompatible polymer, the extent of modification, and the conditions for modification of a therapeutic agent with a biocompatible polymer to prevent host-mediated inactivation of said therapeutic agent when covalently modified by said biocompatible polymer. The method includes the steps of:

(a) assaying a first blood sample from a first immunocompetent subject for a biological activity of a first modified therapeutic agent after said first modified therapeutic agent has been administered to said first immunocompetent subject, wherein said first modified therapeutic agent is covalently modified with a biocompatible polymer;

(b) assaying a second blood sample from said first immunocompetent subject for the biological activity of said first modified therapeutic agent after at least one booster dose of

said first modified therapeutic agent has been administered to said first immunocompetent subject;

(c) assaying a third blood sample from a second immunocompetent subject for the biological activity of a second modified therapeutic agent after said second modified therapeutic agent has been administered to said second immunocompetent subject, wherein said second modified therapeutic agent is covalently modified with a biocompatible polymer and wherein at least one condition selected from the group consisting of the type of biocompatible polymer, the extent of modification, and the conditions for modification differs from the conditions of said first modified therapeutic agent;

(d) assaying a fourth blood sample from said second immunocompetent subject for the biological activity of said second modified therapeutic agent after at least one booster dose of said second modified therapeutic agent has been administered to said second immunocompetent subject; and

(e) comparing the biological activity of said first modified therapeutic agent with the biological activity of said second modified therapeutic agent to select the type of biocompatible polymer, the extent of modification, and the conditions for modification that prevent host-mediated inactivation of said therapeutic agent when covalently modified by said biocompatible polymer,

wherein said therapeutic agent comprises an enzyme and said biological activity comprises an enzyme catalyzing a reaction, and

wherein said assaying comprises measuring the extent to which said first modified therapeutic agent and said second modified therapeutic agent catalyze a reaction. *See* Specification, page 13, lines 4- 26 and page 21, line 7 to page 23, line 7. In some aspects, the biocompatible polymer can be a polyethylene glycol ("PEG") which is selected from the group consisting of mono-methoxy succinimidyl butanoate (SBA)-PEG, succinimidyl carbonate (SC)-PEG, aldehyde (ALD)-PEG, and succinimidyl propionate (SPA)-PEG. *Id.* at page 15, lines 12-20.

Caim 17 depends from claim 1 and concerns a method of preparing a pharmaceutical composition where host-mediated inactivation is prevented. The inventive method comprises selecting the type of biocompatible polymer, the extent of modification, and the conditions

for modification of a therapeutic agent by the method of claim 1 and modifying said therapeutic agent according to the type of biocompatible polymer, the extent of modification, and the conditions for modification selected. *Id.* at page 18, lines 4-6 and page 23, lines 1-7.

Independent claim 42 is directed to a method for determining the type of biocompatible polymer, the extent of modification, and the conditions for modification of a therapeutic agent with a biocompatible polymer to prevent host-mediated inactivation of said therapeutic agent when covalently modified by said biocompatible polymer, comprising:

(a) selecting a biological activity;

(b) assaying a first blood sample from a first immunocompetent subject for the selected biological activity of step (a) of a first modified therapeutic agent after said first modified therapeutic agent has been administered to said first immunocompetent subject, wherein said first modified therapeutic agent is covalently modified with a biocompatible polymer;

(c) assaying a second blood sample from said first immunocompetent subject for the selected biological activity of step (a) of said first modified therapeutic agent after at least one booster dose of said first modified therapeutic agent has been administered to said first immunocompetent subject;

(d) assaying a third blood sample from a second immunocompetent subject for the selected biological activity of step (a) of a second modified therapeutic agent after said second modified therapeutic agent has been administered to said second immunocompetent subject, wherein said second modified therapeutic agent is covalently modified with a biocompatible polymer and wherein at least one condition selected from the group consisting of the type of biocompatible polymer, the extent of modification, and the conditions for modification differs from the conditions of said first modified therapeutic agent;

(e) assaying a fourth blood sample from said second immunocompetent subject for the selected biological activity of step (a) of said second modified therapeutic agent after at least one booster dose of said second modified therapeutic agent has been administered to said second immunocompetent subject; and

(f) comparing the selected biological activity of step (a) of said first modified therapeutic agent with the selected biological activity of step (a) of said second modified

therapeutic agent to select the type of biocompatible polymer, the extent of modification, and the conditions for modification that prevent host-mediated inactivation of said therapeutic agent when covalently modified by said biocompatible polymer,

wherein said therapeutic agent comprises an enzyme and said biological activity comprises an enzyme catalyzing a reaction and

wherein said assaying comprises measuring the extent to which said first modified therapeutic agent and said second modified therapeutic agent catalyze a reaction.
Id. at page 13, lines 4- 26 and page 21, line 7 to page 23, line 7.

Yet another aspect of the presently claimed invention provides, as recited in independent claim 44, a method for determining the type of biocompatible polymer, the extent of modification, and the conditions for modification of a therapeutic agent with a biocompatible polymer to prevent host-mediated inactivation of said therapeutic agent when covalently modified by said biocompatible polymer. The method includes the following steps:

(a) selecting a biological activity;

(b) assaying a first blood sample from a first immunocompetent subject for the selected biological activity of step (a) of a first modified therapeutic agent after said first modified therapeutic agent has been administered to said first immunocompetent subject, wherein said first modified therapeutic agent is covalently modified with a biocompatible polymer;

(c) assaying a second blood sample from said first immunocompetent subject for the selected biological activity of step (a) of said first modified therapeutic agent after at least one booster dose of said first modified therapeutic agent has been administered to said first immunocompetent subject;

(d) assaying a third blood sample from a second immunocompetent subject for the selected biological activity of step (a) of a second modified therapeutic agent after said second modified therapeutic agent has been administered to said second immunocompetent subject, wherein said second modified therapeutic agent is covalently modified with a biocompatible polymer and wherein at least one condition selected from the group consisting

of the type of biocompatible polymer, the extent of modification, and the conditions for modification differs from the conditions of said first modified therapeutic agent;

(e) assaying a fourth blood sample from said second immunocompetent subject for the selected biological activity of step (a) of said second modified therapeutic agent after at least one booster dose of said second modified therapeutic agent has been administered to said second immunocompetent subject;

(f) comparing the selected biological activity of step (a) of said first modified therapeutic agent with the selected biological activity of step (a) of said second modified therapeutic agent to determine the relative bioavailability of said first modified therapeutic agent and said second therapeutic agent; and

(g) selecting the type of biocompatible polymer, the extent of modification, and the conditions for modification that prevent host-mediated inactivation of said therapeutic agent when covalently modified by said biocompatible polymer based upon the comparison of step (f),

wherein said therapeutic agent comprises an enzyme and said biological activity comprises an enzyme catalyzing a reaction and

wherein said assaying comprises measuring the extent to which said first modified therapeutic agent and said second modified therapeutic agent catalyze a reaction. *Id.*

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The issues on appeal are: whether claims 1-3, 5-6, 12, 13, 17, 18, 41, 42, and 44 are unpatentable under 35 U.S.C. § 103(a) over the combination of Boos *et al.*, Kawashima *et al.*, Ettinger *et al.*, Saito *et al.*, and Francis *et al.*; whether claim 4 is unpatentable under 35 U.S.C. § 103(a) over the combination of Boos *et al.*, Kawashima *et al.*, Ettinger *et al.*, Saito *et al.*, Francis *et al.* and Petersen et al.; whether claims 8, 11 and 20-22 are unpatentable under 35 U.S.C. § 103(a) over the combination of Boos *et al.*, Kawashima *et al.*, Ettinger *et al.*, Saito *et al.*, Francis *et al.*, and Abuchowski *et al.*; and whether claim 19 is unpatentable under 35 U.S.C. § 103(a) over the combination of Boos *et al.*, Kawashima *et al.*, Ettinger *et al.*, Saito *et al.*, Francis *et al.* and Bollin *et al.*

VII. ARGUMENT

A. Background

As appellant emphasized in a first appeal involving the present application, the claimed invention relates to determining the modification conditions that protect therapeutic compositions from what is called "host-mediated inactivation." That is, when a host encounters a foreign agent in its circulation, the host's immune system may initiate an immune response. This response includes the production of agent-inactivating antibodies that also enable the reticuloendothelial system to clear the agent from circulation.

Thus, the therapeutic life of an administered non-human agent often is limited by the host's immune system. Furthermore, the problem of host-mediated defense limits the usefulness of human proteins that either are not generally found in circulation or are produced in heterologous systems, using recombinant DNA technology. See Specification, page 1, lines 7-14.

Before appellant's work, various methods looked at biological response to an agent in a treated subject, namely immunogenicity which is assumed to correlate with the loss of functional activity or antigenicity which compares the extent of shielding of the compound by the modifying agent to biological response to the unmodified agent. In these methods, however, functional activity of the biological agent was in fact determined before administration in order to determine the loss of acceptable activity which, to the most part, determined the extent to which a compound can be modified. This is very different, however, from the functional activity recovered after the administration of the modified biological agent to a subject as described by appellant in the present application.

The existing criteria -- antigenicity, immunogenicity, and acceptable loss of bioactivity -- for determining the activated PEG used and the extent of PEGylation are insufficient for ascertaining the modification for an agent in instances where such agents are administered to a patient over a prolonged period of time. This is true because none of the foregoing criteria takes into consideration the effect of the host's response on the agent's biological activity after the PEGylated agent is administered to the host.

Consequently, reliance in the art on the aforementioned criteria yielded an agent that was not optimally protected from the host's immune system or otherwise from *in situ* inactivation. See Specification, page 2, lines 16-23. Accordingly, there is a great and present need for a strategy that would enable the skilled artisan to determine the extent of modification for a given agent that is administered to a patient during prolonged periods of therapy.

Appellant discovered that, when a novel, physiologically relevant optimization scheme is applied and the modifying agent is a polyethylene glycol, these modification ("PEGylation") ranges are not commensurate with the highest suitable PEGylation range, as determined by employing an in vitro assay that monitors loss of therapeutic activity, antigenicity, and immunogenicity. Appellant's discovery suggests that over-PEGylation of an agent, as well as over-modification of an agent with any modifying agent, can disrupt the secondary and/or tertiary structure of the agent, thus exposing new antigenic determinants to the immune system. This observation applies equally to other bio-compatible polymers or agents used to increase the useful circulating half-life of therapeutic agents. See Specification, page 2, line 24 – page 3, line 8.

The invention of the appealed claims addresses this need by providing methodology for determining the optimal modification of an enzymatic therapeutic agent, such that it retains its functional activity over the course of therapy that might well involve repeated administration. Appellant accomplished this by measuring, from samples obtained from the test subject, the ability of the modified enzyme to catalyze a reaction after the first and subsequent administrations so as to determine the extent of modification that best preserves the functional activity after repeated administration.

In asserting that the prior art renders the claimed invention obvious, the examiner points to diverse aspects of various published documents with no apparent rationale for combining them in the fashion claimed, save appellant's own disclosed insights. Thus, a *prima facie* case of obviousness has not been established. Furthermore, in trying to justify the rejection, the examiner proposes to construe the claims in a manner inconsistent with controlling case law, thereby committing additional legal errors.

B. Rejection under 35 U.S.C. § 103(a) over Boos *et al.*, Kawashima *et al.*, Ettinger *et al.*, Saito *et al.*, and Francis *et al.*

1. Claims 1-3, 5-6, 12, 13, 17, 18, 41, 42, and 44

The examiner attempts to recreate appellant's invention from diverse aspects of various published documents, spanning nearly a decade. Thus, from the cited references the examiner cherry-picks various steps used to determine the modification conditions of a therapeutic agent from among countless possible combinations. Nothing in the cited record, however, suggests which parameters are critical or which of many possible choices is likely to be successful for determining the modification conditions of a therapeutic agent to prevent host-mediated inactivation of the therapeutic agent.

The examiner cites Boos for allegedly "stud[ying] the effects of using *unmodified* asparaginase from *different* sources, (*E. coli* or *Erwinia*) in the *treatment* of acute lymphoblastic leukemia" and using "asparaginase activity [as] the primary parameter for monitoring the effect of the drug on *patients*". Office Action dated June 23, 2009, pg. 3 (emphasis added). In addition, the examiner cites Kawashima and Ettinger for allegedly teaching a method of determining activities *in vivo* of PEG2-ASP or PEG-L-asparaginase, respectively, after and between multiple administrations of the respective drugs. Saito is cited for teaching the antitumor activity of PM-asparginase relative to unmodified asparaginase. Finally, the examiner invokes the alleged disclosure by Francis that the degree of PEGylation is determined empirically by examining a range of different degrees of substitution and coupling techniques.

To justify his tying the references together in this manner, the examiner asserts that "it would have been obvious": (1) to compare the efficacies of each of the different L-asparginase forms, in order to see which performed best in treating a given disease; (2) to use the protocols of Kawashima and Boos to measure the catalytic activity of the enzyme throughout the course of treatment; and (3) to perform the comparisons of activity *in vivo*. *Id.* at page 6. To support this "just so" sequence of inferences, the examiner relies upon Boos for allegedly "providing a template for comparing different preparations of asparaginase," thereby supplying a motivation for the skilled artisan to use enzymatic activity as the metric

by which to optimize the protection of an enzymatic therapeutic agent against host-mediated inactivation. *Id.* at paragraph spanning pgs. 5-6.

In so doing, the examiner presumes the very insight that appellant's own discovery illuminated. Such a presumption is the hallmark of hindsight reconstruction and cannot support a prima facie case of obviousness. *In re Lee*, 277 F.3d 1338, 1344 (Fed. Cir. 2002) ("It is improper, in determining whether a person of ordinary skill would have been led to this combination of references, simply to '[use] that which the inventor taught against its teacher'"), *citing W.L. Gore v. Garlock, Inc.*, 721 F.2d 1540, 1553 (Fed. Cir. 1983).

A more critical reading of Boos shows the authors evaluated the known variability in activity among different commercial preparations of asparaginase by monitoring, among other things, asparaginase activity during the course of therapy of 56 children and, thereby, formulated dosing recommendations for each commercial preparation. For instance, *see* Boos *et al.* at page 1545, column 1, in the 1st full paragraph, and at page 1549. It is hardly surprising that a practitioner formulated dose-response curves in an effort to formulate a uniform dosing regime for an enzymatic therapy. Nothing in the cited materials, however, suggests that such testing should be applied in the preclinical setting of research and development, as the examiner contends. Indeed, the examiner's assertion about what a skilled person conceivably might have been motivated to do in a preclinical setting belies what artisans before the present invention actually did.

From the various documents cited previously against the claimed invention, such as Chinol *et al.*, Deckert *et al.* and Alvarez *et al.* (attached herewith as Exhibits A-C, respectively), it is clear that practitioners in the relevant field, circa 2000, sought during preclinical development to optimize therapeutic agents against host-mediated inactivation by examining the impact of antigenicity, immunogenicity, and acceptable loss of bioactivity. *See also* Appeal Brief, filed November 10, 2006, at pg. 2-5 and 10-13. Thus, conventional wisdom regarding therapeutic protein optimization focused upon shielding the therapeutic protein from the immune system and increasing the protein's stability. *See, e.g.,* Specification, pg. 1, ln. 7 to pg. 3, ln. 8.

By the same token, one of appellant's insights was to abandon convention and optimize the modification a therapeutic enzyme by evaluating, after *in vivo* administration,

the modified enzyme's capacity to catalyze its reaction. Now, the examiner attempts to use that very insight against appellant to suggest a basis for why one of ordinary skill might have combined the cited references. Such a *post hoc* rationale cannot support a *prima facie* case of obviousness, however. *See In re Lee*, 277 F.3d at 1344.

Apparently recognizing this error, the examiner now attempts through creative claim construction to eliminate this aspect from claim 1, which is further legal error. That is, in an effort to minimize the gulf between appellant's invention and the cited art, the examiner seeks to transform the claimed invention from its developmental setting of optimizing the modification a therapeutic enzyme to that of the clinical setting, where the therapeutic benefit of candidate compounds is assessed. To bring about this transformation, the examiner, when construing the pending independent claims, purposely gives no patentable weight (1) to the phrase "to select the type of biocompatible polymer, the extent of modification, and the conditions for modification that prevent host-mediated inactivation of said therapeutic agent when covalently modified by said biocompatible polymer" or (2) the preamble. *See* Examiner's Answer, pg. 12, ¶¶ 1-2. Both constructions are legally flawed, however.

In attempting to eliminate the "selection" aspect from claim 1, the examiner asserts that the clause "receives no patentable weight because it is not an active step, and merely represents something that is inherent in the active step of comparing the agents." Examiner's Answer, pg. 12, ¶1. It is not surprising that no authority is cited for this assertion. Indeed, it contravenes the presumption that "all claim terms are presumed to have meaning in a claim". *See Innova/Pure Water, Inc. v. Safari Water Filtration Sys.*, 381 F.3d 1111, 1119 (Fed. Cir. 2004) (rejecting a proposed construction that read out of the claims a term describing the intended use). *See also Bicon, Inc. v. Straumann Co.*, 441 F.3d 945, 950 (Fed. Cir. 2006) "claims are interpreted with an eye toward giving effect to all terms in a claim"). In the instant case, the cited infinitive phrase functions as an adverb explaining why the comparison is made and instructing the actor what to do with the data obtained from the prior steps. Accordingly, to read the phrase out of claim 1 constitutes legal error.

The examiner's attempt to disregard the preamble of the independent claims is similarly flawed. The determination of whether a preamble limits a claim is made on a case-by-case basis in light of the facts in each case. *Catalina Mktg. Int'l v. Coolsavings.com, Inc.*,

289 F.3d 801, 808 (Fed. Cir. 2002). In general, a preamble limits the invention if it is "necessary to give life, meaning, and vitality" to the claim. *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305 (Fed. Cir. 1999). *See also Jansen v. Rexall Sundown, Inc.*, 342 F.3d 1329, 1333 (Fed. Cir. 2003). Moreover, the Federal Circuit has emphasized the importance of attributing patentable weight to a preamble where applicant has relied upon the preamble's statement of intended use for distinguishing the prior art. *Metabolite Labs., Inc. v. Corp. of Am. Holdings*, 370 F.3d 1354, 1362 (Fed. Cir. 2004).

For each of the rejected claims, consideration of the preamble gives meaning and purpose to the recited manipulative steps. In the absence of the preamble's stated objective of "determining the type of biocompatible polymer, the extent of modification, and the conditions for modification of a therapeutic agent with a biocompatible polymer to prevent host-mediated inactivation of said therapeutic agent when covalently modified by said biocompatible polymer", the recited "assaying" and "comparing" terms resolve to mere academic exercises. *Compare Griffin v. Bertina*, 285 F.3d 1029, 1033 (Fed. Cir. 2002)(giving limiting effect to the preamble where it gave meaning and purpose to the recited manipulative steps). Indeed, the manipulative steps set forth in the claims have little meaning or utility unless they are placed within the context of optimizing therapeutic agents against host-mediated inactivation, as recited in the preamble. *Id.* at 1034. *See also Jansen v. Rexall Sundown, Inc.*, 342 F.3d 1329, 1333-34 (Fed. Cir. 2003) (giving limiting effect to the preamble where it recited the intentional purpose for performing the method). Furthermore, in distinguishing cited art, appellant has emphasized repeatedly that the claimed invention concerns optimizing therapeutic agents against host-mediated inactivation, as recited in the preamble. *See, e.g.* Amendment and Reply filed May 20, 2009, pg. 13, ¶ 4 and pg. 15, ¶ 2. Amendment and Reply filed December 4, 2008, pg. 11, ¶ 6 and pg. 12, ¶ 2. *Metabolite Labs.*, 370 F.3d at 1362.

Accordingly, it constitutes legal error to give no patentable weight to the preamble of the rejected claims.

More broadly, therefore, the examiner's attempt to recreate appellant's invention from among diverse aspects of various published documents falls well short of his burden when rejecting claims under §103. Importantly, the examiner has not shown an apparent reason to

have combined the various prior-art elements in the fashion claimed, with the requisite expectation of success. *Compare KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1740-1741 (2007). In applying *KSR*, moreover, the Federal Circuit has found non-obviousness where the claims at issue were directed to a specific chemical compound and "the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation." *Takeda Chem. Industs., Ltd. v. Alphapharm Pty, Ltd.*, 492 F.3d 1350 (Fed. Cir. 2007). *See also Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc.*, 520 F.3d 1358 (Fed. Cir. 2008).

As in the *Takeda* case, the cited references here disclose a number of possible steps but provide no reason for selecting the particular combination of appellant's claimed methodology. For example, the cited references teach a variety of ways for measuring enzyme activity, most of which are indirect measurements unsuitable for gauging the biological activity of a modified therapeutic agent. *See* Declaration of Natarajan Sethuraman, ¶ 6, a copy of which is attached herewith as Exhibit D.

Similarly, the cited material presents a myriad of timing options for conducting measurements. For the timing components recited in the claims, the examiner points to Kawashima for allegedly teaching the evaluation of modified therapeutic agents "before, after and between multiple administrations" and Boos for monitoring activity throughout the course of treatment. Examiner's Answer, pg. 4, ¶ 1, and pg. 6, ¶ 1. Kawashima and Boos, of course, were not optimizing the modification level of a therapeutic agent. Rather, they simply monitored the effects of administered drugs over courses of therapy. Nothing in the cited material, therefore, hints of a method of determining the modification conditions of a therapeutic agent to prevent host-mediated inactivation where a therapeutic agent is modified in two different ways and the biological activities of the two modified agents are compared *after each modified agent has been administered at least twice*.

The examiner's approach here mirrors what the Federal Circuit condemned in *Ortho-McNeil*. In that case the court considered an obviousness analysis performed by a technical expert during trial. *Ortho-McNeil Pharmaceutical, Inc.*, 520 F.3d at 1364. In particular, the court admonished the expert for "simply retrac[ing] the path of the inventor with hindsight, discount[ing] the number and complexity of the alternatives, and conclud[ing] that the

invention [ ] was obvious." *Id.* Like the expert in *Ortho-McNeil*, the examiner has recreated applicants' invention using hindsight and discounted the number and complexity of the alternatives. *Compare* MPEP § 2142 ("tendency to resort to 'hindsight' ... is often difficult to avoid ... [and yet] impermissible hindsight must be avoided and the legal conclusion must be reached on the basis of the facts gleaned from the prior art").

Accordingly, the examiner's combination of references does not provide the required reason to combine the selected portions of the cited references to produce the claimed invention. Thus, a *prima facie* case of obviousness has not been established. Appellant respectfully requests, therefore, that the rejection be overruled.

2. Claims 17 and 44

The aberrant claim constructions proposed by the examiner to deny the existence of a selection component to the claimed methods ring even more hollow with respect to claims 17 and 44. Beyond the reasons noted above, claims 17 and 44 specifically comprise steps requiring a "selecti[ion of] the type of biocompatible polymer,...etc." based upon the assaying and comparing steps of the claimed methods. Accordingly, the examiner's denial of this feature from these claims is legally untenable. For this reason, as well, appellant respectfully requests that the rejections with respect to claims 17 and 44 be overruled.

C. Rejection Under 35 U.S.C. § 103(a) over Boos *et al.*, Kawashima *et al.*, Ettinger *et al.*, Saito *et al.*, Francis *et al.* and Petersen *et al.*

The teachings and short-comings of Boos *et al.*, Kawashima *et al.*, Ettinger *et al.*, Saito *et al.*, Francis *et al.* are discussed above in Section VII.B., and the arguments presented there are herein incorporated by reference. The examiner cites Peterson, meanwhile, for allegedly teaching SBA-, SC-, and ALD-PEGs and other types of modified PEGs. Office Action mailed June 23, 2009, pg. 8, ¶1. The cited material in Petersen, however, fails to cure the deficiencies noted for the remaining references.

As noted above, therefore, the examiner has advanced no apparent reason to have combined in the posited fashion the various prior-art elements. Thus, a *prima facie* case of obviousness has not been established. Appellant respectfully requests, therefore, that the rejection be overruled.

D. Rejection Under 35 U.S.C. § 103(a) over Boos *et al.*, Kawashima *et al.*, Ettinger *et al.*, Saito *et al.*, Francis *et al.*, and Abuchowski *et al.*

The teachings and short-comings of Boos *et al.*, Kawashima *et al.*, Ettinger *et al.*, Saito *et al.*, Francis *et al.* are discussed above in Section VII.B., and the arguments presented there are herein incorporated by reference. The examiner cites Abuchowski, meanwhile, for allegedly teaching the treatment of tumors in mice by administration of *Achromobacter* glutaminase asparaginase rendered non-immunogenic by modification with polyethylene glycol. *Id.* at pg. 9, ¶4. The cited material in Abuchowski, however, fails to cure the deficiencies noted for the remaining references.

As noted above, therefore, the examiner has advanced no apparent reason to have combined in the posited fashion the various prior-art elements. Thus, a *prima facie* case of obviousness has not been established. Appellant respectfully requests, therefore, that the rejection be overruled.

E. Rejection Under 35 U.S.C. § 103(a) over Boos *et al.*, Kawashima *et al.*, Ettinger *et al.*, Saito *et al.*, Francis *et al.* and Bollin *et al.*

The teachings and short-comings of Boos *et al.*, Kawashima *et al.*, Ettinger *et al.*, Saito *et al.*, Francis *et al.* are discussed above in Section VII.B., and the arguments presented there are herein incorporated by reference. The examiner cites Bollin, meanwhile, for allegedly teaching that proteins can be stabilized by lyophilization and that saccharides are useful in stabilizing asparaginase during lyophilization. *Id.* at pg. 10, ¶ 5. The cited material in Bollin, however, fails to cure the deficiencies noted for the remaining references.

As noted above, therefore, the examiner has advanced no apparent reason to have combined in the posited fashion the various prior-art elements. Thus, a *prima facie* case of obviousness has not been established. Appellant requests, therefore, that the rejection be overruled.

Respectfully submitted,

Date 26 February 2010 By _____

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (617) 342-4039
Facsimile: (617) 672-4001

R. Brian McCaslin
Attorney for Appellant
Registration No. 48,571

VIII. CLAIMS APPENDIX

1. (Previously Presented) A method for determining the type of biocompatible polymer, the extent of modification, and the conditions for modification of a therapeutic agent with a biocompatible polymer to prevent host-mediated inactivation of said therapeutic agent when covalently modified by said biocompatible polymer, comprising:

(a) assaying a first blood sample from a first immunocompetent subject for a biological activity of a first modified therapeutic agent after said first modified therapeutic agent has been administered to said first immunocompetent subject, wherein said first modified therapeutic agent is covalently modified with a biocompatible polymer;

(b) assaying a second blood sample from said first immunocompetent subject for the biological activity of said first modified therapeutic agent after at least one booster dose of said first modified therapeutic agent has been administered to said first immunocompetent subject;

(c) assaying a third blood sample from a second immunocompetent subject for the biological activity of a second modified therapeutic agent after said second modified therapeutic agent has been administered to said second immunocompetent subject, wherein said second modified therapeutic agent is covalently modified with a biocompatible polymer and wherein at least one condition selected from the group consisting of the type of biocompatible polymer, the extent of modification, and the conditions for modification differs from the conditions of said first modified therapeutic agent;

(d) assaying a fourth blood sample from said second immunocompetent subject for the biological activity of said second modified therapeutic agent after at least one booster dose of said second modified therapeutic agent has been administered to said second immunocompetent subject; and

(e) comparing the biological activity of said first modified therapeutic agent with the biological activity of said second modified therapeutic agent to select the type of biocompatible polymer, the extent of modification, and the conditions for modification that

prevent host-mediated inactivation of said therapeutic agent when covalently modified by said biocompatible polymer,

wherein said therapeutic agent comprises an enzyme and said biological activity comprises an enzyme catalyzing a reaction, and

wherein said assaying comprises measuring the extent to which said first modified therapeutic agent and said second modified therapeutic agent catalyze a reaction.

2. (Previously Presented) The method of claim 1, wherein said second modified therapeutic agent is modified with the same biocompatible polymer as said first modified therapeutic agent.

3. (Previously Presented) The method of claim 2, wherein said biocompatible polymer is polyethylene glycol (PEG).

4. (Original) The method of claim 3, wherein said PEG is selected from the group consisting of mono-methoxy succinimidyl butanoate (SBA)-PEG, succinimidyl carbonate (SC)-PEG, aldehyde (ALD)-PEG, and succinimidyl propionate (SPA)-PEG.

5. (Previously Presented) The method of claim 1, wherein said second modified therapeutic agent is modified to the same extent as said first modified therapeutic agent.

6. (Previously Presented) The method of claim 1, wherein said second modified therapeutic agent and said first modified therapeutic agent are modified with different biocompatible polymers.

7-10. Cancelled.

11. (Previously Presented) The method of claim 1, wherein said enzyme is used to lower glutamine levels in a subject.

12. (Previously Presented) The method of claim 1, wherein said enzyme is used to lower asparagine levels in a subject.

13. (Previously Presented) The method of claim 1, wherein said enzyme is used to lower asparagine and glutamine levels in a subject.

14-16. Cancelled.

17. (Previously Presented) A method of preparing a pharmaceutical composition where host-mediated inactivation is prevented, comprising selecting the type of biocompatible polymer, the extent of modification, and the conditions for modification of a therapeutic agent by the method of claim 1 and modifying said therapeutic agent according to the type of biocompatible polymer, the extent of modification, and the conditions for modification selected.

18. (Original) The method of claim 17, wherein said pharmaceutical composition further comprises an excipient.

19. (Original) The method of claim 18, wherein said excipient protects said therapeutic agent during lyophilization.

20. (Original) The method of claim 17, wherein said therapeutic agent comprises glutaminase-asparaginase.

21. (Previously Presented) The method of claim 20, wherein said therapeutic agent comprises *Pseudomonas* glutaminase-asparaginase.

22. (Original) The method of claim 21, wherein said *Pseudomonas* glutaminase-asparaginase is modified with polyethylene glycol.

23-40 Cancelled.

41. (Previously Presented) The method of claim 1, wherein said second immunocompetent subject is the same person as said first immunocompetent subject.

42. (Previously Presented) A method for determining the type of biocompatible polymer, the extent of modification, and the conditions for modification of a therapeutic agent

with a biocompatible polymer to prevent host-mediated inactivation of said therapeutic agent when covalently modified by said biocompatible polymer, comprising:

(a) selecting a biological activity;

(b) assaying a first blood sample from a first immunocompetent subject for the selected biological activity of step (a) of a first modified therapeutic agent after said first modified therapeutic agent has been administered to said first immunocompetent subject, wherein said first modified therapeutic agent is covalently modified with a biocompatible polymer;

(c) assaying a second blood sample from said first immunocompetent subject for the selected biological activity of step (a) of said first modified therapeutic agent after at least one booster dose of said first modified therapeutic agent has been administered to said first immunocompetent subject;

(d) assaying a third blood sample from a second immunocompetent subject for the selected biological activity of step (a) of a second modified therapeutic agent after said second modified therapeutic agent has been administered to said second immunocompetent subject, wherein said second modified therapeutic agent is covalently modified with a biocompatible polymer and wherein at least one condition selected from the group consisting of the type of biocompatible polymer, the extent of modification, and the conditions for modification differs from the conditions of said first modified therapeutic agent;

(e) assaying a fourth blood sample from said second immunocompetent subject for the selected biological activity of step (a) of said second modified therapeutic agent after at least one booster dose of said second modified therapeutic agent has been administered to said second immunocompetent subject; and

(f) comparing the selected biological activity of step (a) of said first modified therapeutic agent with the selected biological activity of step (a) of said second modified therapeutic agent to select the type of biocompatible polymer, the extent of modification, and the conditions for modification that prevent host-mediated inactivation of said therapeutic agent when covalently modified by said biocompatible polymer,

wherein said therapeutic agent comprises an enzyme and said biological activity comprises an enzyme catalyzing a reaction and

wherein said assaying comprises measuring the extent to which said first modified therapeutic agent and said second modified therapeutic agent catalyze a reaction.

43. Cancelled.

44. (Previously Presented) A method for determining the type of biocompatible polymer, the extent of modification, and the conditions for modification of a therapeutic agent with a biocompatible polymer to prevent host-mediated inactivation of said therapeutic agent when covalently modified by said biocompatible polymer, comprising:

(a) selecting a biological activity;

(b) assaying a first blood sample from a first immunocompetent subject for the selected biological activity of step (a) of a first modified therapeutic agent after said first modified therapeutic agent has been administered to said first immunocompetent subject, wherein said first modified therapeutic agent is covalently modified with a biocompatible polymer;

(c) assaying a second blood sample from said first immunocompetent subject for the selected biological activity of step (a) of said first modified therapeutic agent after at least one booster dose of said first modified therapeutic agent has been administered to said first immunocompetent subject;

(d) assaying a third blood sample from a second immunocompetent subject for the selected biological activity of step (a) of a second modified therapeutic agent after said second modified therapeutic agent has been administered to said second immunocompetent subject, wherein said second modified therapeutic agent is covalently modified with a biocompatible polymer and wherein at least one condition selected from the group consisting of the type of biocompatible polymer, the extent of modification, and the conditions for modification differs from the conditions of said first modified therapeutic agent;

(e) assaying a fourth blood sample from said second immunocompetent subject for the selected biological activity of step (a) of said second modified therapeutic agent after at least one booster dose of said second modified therapeutic agent has been administered to said second immunocompetent subject;

(f) comparing the selected biological activity of step (a) of said first modified therapeutic agent with the selected biological activity of step (a) of said second modified therapeutic agent to determine the relative bioavailability of said first modified therapeutic agent and said second therapeutic agent; and

(g) selecting the type of biocompatible polymer, the extent of modification, and the conditions for modification that prevent host-mediated inactivation of said therapeutic agent when covalently modified by said biocompatible polymer based upon the comparison of step (f),

wherein said therapeutic agent comprises an enzyme and said biological activity comprises an enzyme catalyzing a reaction and

wherein said assaying comprises measuring the extent to which said first modified therapeutic agent and said second modified therapeutic agent catalyze a reaction.

45-46. Cancelled.

47. (Withdrawn) The pharmaceutical composition prepared by the method of claim 17, wherein said pharmaceutical composition comprises a glutaminase-asparaginase that has been modified with succinimidyl carbonate polyethylene glycol 5000 (SC-PEG 5000), wherein said glutaminase-asparaginase is modified to an extent of from about 21% to about 49% by SC-PEG 5000, and wherein said composition prevents host-mediated inactivation.

48. (Withdrawn) The composition of claim 47, wherein said glutaminase-asparaginase is modified from about 26% to about 36% by SC-PEG 5000.

49. (Withdrawn) The composition of claim 48, wherein said glutaminase-asparaginase is modified about 31% by SC-PEG 5000.

50. (Withdrawn) The pharmaceutical composition prepared by the method of claim 17, wherein said pharmaceutical composition comprises a glutaminase-asparaginase that has been modified with mono-methoxy succinimidyl butanoate polyethylene glycol 5000 (SBA-PEG 5000), wherein said glutaminase-asparaginase is modified from about 25% to about 58% by SBA-PEG 5000, and wherein said composition prevents host-mediated inactivation.

51. (Withdrawn) The composition of claim 50, wherein said glutaminase-asparaginase is modified from about 30% to about 40% by SBA-PEG 5000.

52. (Withdrawn) The composition of claim 51, wherein said glutaminase-asparaginase is modified about 35% by SBA-PEG 5000.

53. (Withdrawn) The pharmaceutical composition prepared by the method of claim 17, wherein said pharmaceutical composition comprises a glutaminase-asparaginase that has been modified with aldehyde polyethylene glycol 2000 (ALD-PEG 2000), wherein said glutaminase-asparaginase is modified from about 45% to about 65% by ALD-PEG 2000, and wherein said composition prevents host-mediated inactivation.

54. (Withdrawn) The pharmaceutical composition prepared by the method of claim 17, wherein said pharmaceutical composition comprises a glutaminase-asparaginase that has been modified with succinimidyl propionate polyethylene glycol 5000 (SPA-PEG 5000), wherein said modified glutaminase-asparaginase is modified from about 25% to about 65% by SPA-PEG 5000, and wherein said composition prevents host-mediated inactivation.

55. (Withdrawn) The composition of claim 54, wherein said glutaminase-asparaginase is modified from about 40% to about 55% by SPA-PEG 5000.

56. (Withdrawn) A composition comprising a glutaminase-asparaginase, wherein said glutaminase-asparaginase has been modified with succinimidyl carbonate polyethylene glycol 5000 (SC-PEG 5000) to an extent of about between 21% and 49%.

57. (Withdrawn) The modified therapeutic composition of claim 56, wherein said glutaminase-asparaginase has been modified to an extent of about between 26% and 36%.

58. (Withdrawn) The modified therapeutic composition of claim 57, wherein said glutaminase-asparaginase has been modified to an extent of about 31%.

59. (Withdrawn) A composition comprising a glutaminase-asparaginase, wherein said glutaminase-asparaginase has been modified with succinimidyl butanoate polyethylene glycol 5000 (SBA-PEG 5000) to an extent of about between 25% and 58%.

60. (Withdrawn) The modified therapeutic composition of claim 59, wherein said glutaminase-asparaginase has been modified to an extent of about 30% to 40%.

61. (Withdrawn) The modified therapeutic composition of claim 36, wherein said glutaminase-asparaginase has been modified to an extent of about 35%.

62. (Withdrawn) A composition comprising a glutaminase-asparaginase, wherein said glutaminase-asparaginase has been modified with aldehyde polyethylene glycol 2000 (ALD-PEG 2000) to an extent of about between 45% and 65%.

63. (Withdrawn) A composition comprising a glutaminase-asparaginase, wherein said glutaminase-asparaginase has been modified with succinimidyl propionate polyethylene glycol 5000 (SPA-PEG 5000) to an extent of about between 25% and 65%.

64. (Withdrawn) The modified therapeutic composition of claim 63, wherein said glutaminase-asparaginase has been modified to an extent of about 40% to 55%.

IX. EVIDENCE APPENDIX

Exhibit A. Chinol *et al.*, British Journal of Cancer 78(2): 189-197 (1998), which was cited by the examiner in the Office Action mailed April 6, 2005 at pg. 4.

Exhibit B. Deckert *et al.*, Int. Journal of Cancer 87:382-390 (2000), which was cited by the examiner in the Office Action mailed April 6, 2005 at pg. 4.

Exhibit C. Alvarez *et al.*, Med. Pediatr. Oncol. 34(3):200-205 (2000), which was cited by the examiner in the Office Action mailed January 29, 2004 at pg. 5.

Exhibit D. Declaration of Natarajan Sethuraman, ¶ 6, which was filed on December 4, 2008 and acknowledged by the examiner in the Office Action mailed on February 20, 2009 at pg. 17.

X. RELATED PROCEEDINGS APPENDIX

None.